

Limitations on Dose Estimation

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The process of estimation of dose at a target organ from the measurements of environmental concentration of potentially hazardous agents is theoretically examined. The analysis of the estimation process suggests that the design of any study which aims to find the health effects of an agent or to construct a dose-response relationship from environmental measurements must be fully scrutinized to see whether a representative dose is tractable from such measurements made on the agent or extrapolation from a set of known effects at high dose levels is feasible and desirable.

Introduction

Even under the most generalized definition of health, the relationship between the environment and health may be characterized by a series of responses elicited due to the presence of causal agents. Furthermore, inherent in this relationship is the specific definition of a deleterious health effect by the magnitude of a set of acute, chronic or residual responses. Consequently, the toxicological or the epidemiological assessment of an effect or the regulatory steps taken to control a deleterious effect depend on the understanding and the prediction of responses under varied concentrations and conditions of the causative and the contributory agents in specific environments.

An agent, in order to elicit a response, must reach a critical site in the body in a form which will cause the response. Furthermore, the specific amount of the challenge must be at a dose level associated with the response. Clearly, the response of each individual to a given dose is an individual function strongly influenced by the biological variability between individuals. Although the problems associated with the biological variability are complicated, if the first independent variable of the relationship, dose, can be quantified, then the response to such a dose can also be quantified within the associated individual biological

variability. In a study, dose is measured only on rare occasions under well controlled experimental situations. Normally, dose is estimated under a set of tacit or stated assumptions from exposure or estimation of exposure. Consequently, in a given study, the process of estimation of dose may become such an integral part of the estimated doses that the possible interrelationship developed between the estimated doses and measured responses would be fortuitous. Therefore, a formal investigation of this estimation process is helpful in defining the general limitations under which the construction of dose response relationships must operate. The dose estimation process is a complicated one, and it depends upon a number of distinct transformations, some of which are poorly understood. This difficulty may be overcome by the introduction of a formalistic approach. In this paper such a formalism is presented and analyzed.

Before the theoretical treatment is presented, let us set the stage with a numerical example. Suppose two communities are selected for an epidemiological study on the effect of cadmium exposure on hypertension. In both communities the cohort selected is from households which contain no smokers and no member of the cohort has any known industrial exposure to cadmium. In both communities, only airborne cadmium levels are measured daily in sufficient locations. Now let us suppose that in community A the range of airborne cadmium concentration level is 0.01 to 0.03 $\mu\text{g}/\text{m}^3$, and in community B the corresponding measure is 0.04 to 0.06 $\mu\text{g}/\text{m}^3$ over one year of

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measurements. Let us further suppose that there is no reason to believe that these levels are significantly different from the levels of past 30 years. Let us suppose that community B shows a significant increase in age-adjusted hypertension as compared to community A. In this seemingly well controlled study, is it really justifiable to attribute the measured excess in hypertension to the measured difference in the airborne cadmium concentration levels? If we do so, we tacitly assume that the total body burden is well estimated by the measurements of airborne cadmium concentration. This assumption needs to be scrutinized. It is normally expected that the intake of cadmium through drinking water would be 0.2 µg/day and through food would be 10-200 µg/day. Consequently, the total exposure would be totally dominated by food or food and water intake. There is, however, a further complicating factor. It is known that the absorption of cadmium from the lung and from the gut has significantly different efficiencies. It is estimated that only 3 to 20% of dietary cadmium intake is absorbed, whereas 20 to 100% of inhaled cadmium is absorbed, depending on the inhaled particle size spectrum and the particle chemistry. In other words, the contribution of the airborne cadmium may range from equivalent to insignificant as compared to the contribution of dietary intake so far as the dose is concerned. If the airborne level has a very small contribution, dietary differences would dominate the exposure, and conversely the airborne level may be a good indicator. Our inability to make a direct judgement on these two possibilities suggests a set of limitations on the estimation of dose, and we shall focus on these limitations.

Mathematical Model for Dose Estimation

Dose as defined by the amount of an agent or agent derivative at the critical organ, is a scalar quantity which is rarely directly measured under realistic conditions. In general, concentration of the agent is measured in a given set of carriers of the agent external to the body. The obvious examples of these measurements may be given as air concentration, water concentration and so on. In order to achieve full generality, we have to further specify the location of concentration measurement as a function of time. Such as airborne concentration of agent at work place, ambient airborne concentration, and so on. Therefore, concentration C is an n -dimensional vector represent-

ing the presence of the agent in n distinct spaces as a function of time. Each component of C may be quantified at arbitrarily selected sufficient number points of such spaces and time to give the space time distribution of C . The vector C exists independent of the presence of the individual in question; therefore, the exposure of the individual E , as defined by the presence of the agent in contact with the body in corresponding subspaces of C is also an n -dimensional vector generated by a transformation of C by an $n \times n$ dimensional matrix A . Since the transformation matrix A uniquely defines the exposure vector E , formally we represent the relationship as:

$$E = A \otimes C \quad (1)$$

where \otimes represents matrix multiplication.

Although exposure describes the probability of entry into the body, in general, it does not quantify intake. Intake may be defined as the entry through a specific route. That is, for each route of entry C , there exists an n -dimensional weighting vector W_i , such that each component of W_i represents the proper weighting factor of entry through that specific route, for the corresponding component of E . Consequently, a scalar value of intake through each route i may be represented as:

$$b_i = E \cdot W_i \quad (2)$$

The amount of the agent entered through each route i , is further modified by a scalar function η_i , which for each route represents the internal modification and transport to the critical site including reactions, excretion, absorption and so on. For convenience we shall refer to this function as route specific transport efficiency. Since the variables we defined are in a complete normal linear metric space (Banach space), then the total dose over a time interval $(0, T)$ for K routes of entry may be represented by the integral (Lebesgue):

$$D = \int_{(0, T)} \sum_i^k (A \otimes C \cdot W_i) \eta_i \quad (3)$$

We can readily generalize this for a population by requiring the dose for each individual to belong to the distribution of the doses in the population. That is the generated distribution of dose in the population is the mapping of the integral in Eq. (3) onto a one-dimensional space where each estimate \hat{D}_{ij} is a random sample based on j determinations.

We can define the efficacy of the estimation

process by a term we introduce as relative consistency: for any small δ , $\epsilon > 0$, if

$$\Pr[|\hat{\theta}(m) - (\theta + \beta)| < \epsilon] < 1 - \delta \quad m > M \quad (4)$$

the estimator is said to be relatively consistent with relative consistency of $\alpha = \|\theta, \beta\|$. That is, as one increases the sample size, a relatively consistent estimator converges to a value β , α distance away from θ . Consequently, if $\alpha = 0$, then the estimator is consistent. If α is unbounded the estimator is inconsistent and if $\alpha/|\theta| \gg 0$ as $n \rightarrow \infty$, the estimator is relatively inconsistent.

Equation (3) is the generalized form of a dose received by an individual, and $\{D\}$ defines the distribution of dose in a population. The time span selected in the definition of specific dose may be short or may be an entire life experience. As an actual estimation process, one looks at a selected set of measurements in conjunction with a selected population to estimate either a dose distribution over a short interval of time (acute) or a dose distribution over a long interval of time (chronic). Consequently, the selection of population at risk as well as the selection of the type and location of the measurements influence the relative consistency of the estimator. Therefore, careful selection of population may be used to make the estimator relatively consistent by choosing a population where most of the elements of the transformation matrix is nearly zero. In addition, a simple linear transformation based on the route specific transport efficiency may also be necessary and, although it necessitates a prior knowledge of the function η , presents no theoretical difficulties. However, the unfortunate consequence of this observation is that as the selection of the populations is made to remove the dominant components of dose in order to study low dose effects, the importance of all remaining components may start to emerge. In these types of situations unless the contribution of each component can be measured the relative consistency of the estimator, albeit of unknown magnitude, deteriorates. This presents an interesting choice between extrapolation of results from relatively consistent high doses and decision making with relatively inconsistent low doses. Since response is a function of dose for any level of consistency, we can expand response in Taylor series at the limit of convergence:

$$R(\hat{D}) = R(D) + \sum_i \frac{[\text{sgn}(\beta - D) \alpha]^i}{i!} \left(\frac{d}{dD} \right)^i R(D) \quad (5)$$

Here the measured response is $R(D)$, and the measured variable is \hat{D} . If the measurements are made in high dose levels with relatively consistent estimates, then we need to know the function of $R(D)$ to extrapolate to low doses. Similarly, if the measurements are made in high or low dose levels with relatively inconsistent estimates, then we still need to know the function $R(D)$ to make the necessary adjustments to obtain the correct response level.

Applications of the Theory

In order to illustrate the properties of the variables suggested above, it is possible to construct several realistic examples. The almost trivial case which applies to many laboratory experiments may be easily constructed. Consider an experiment in which m volunteers orally receive a prescribed amount of a drug normally not found in the environment. In this almost trivial case, we set matrix A to $[1]$; the concentration vector C is one-dimensional with the magnitude corresponding to the amount swallowed. Intake matrix is also one-dimensional and may be made to correspond to the inverse of the body weight of the volunteers. With the assumption that the route specific efficiency function is narrowly distributed among volunteers, the dose received at a prescribed organ is directly estimated and furthermore, under the stated assumption, there is no reason to believe this dose estimator cannot be made as relative consistent as desired by the judicious choice of n .

As a second example, consider a case where chronic health effects of a chemical in an occupational setting is being investigated. For simplicity, we shall assume that for the selected population the considerations vary within fixed orders of magnitude for all components. Let us further assume that the intake is solely through inhalation and inhalation specific efficiency is constant for all people. The description of the components of the variables are given in Table 1. The component a_{11} may be set close to 1 by means of carrying out personal sampling of the workers; therefore, the exposure e may be nearly directly measured. Within the available techniques of characterization of a work place and estimating historical exposures (1, 2) and within limitations of measurement and projection techniques the distribution of $e_1 w_1$ may be estimated. The measurements of C_2 and C_3 and attendant transformations to obtain e_2 and e_3 are generally more complicated and usually more difficult to estimate although for this example, we may assume w_2 and w_3 to be equal to w_1 . For the condition, where $e_1 w_1$ is much greater than the

Table 1. Definition of the variables of the example cited.

Parameter	Variable	Definition
Concentration	C_1	Airborne concentration at the workplace
	C_2	Ambient airborne concentration
	C_3	Home airborne concentration
Transform: a_{ij} , $i \neq j = 0$	a_{11}	Function which relates C_1 to workplace exposure, including time spent at work
	a_{22}	Function which relates C_2 to ambient exposure, including time spent outdoors
	a_{33}	Function which relates C_3 to home exposure, including time spent at home
Exposure	e_1	Workplace exposure
	e_2	Ambient exposure
	e_3	Home exposure
Intake	w_1	Workplace exposure weighing factor, including activity level
	w_2	Ambient exposure weighing factor, including outdoor activity level such as running
	w_3	Home exposure weighing factor, including activity level

sum of the two remaining terms, we can say that the dose is dominated by one component and therefore the integral which represents the estimate of cumulative dose based on this component alone may be gauged to be relatively consistent. As an example, if C_1 is in the order of 10 and C_2 and C_3 are in the order of 10^{-2} , the week (40 hr) of occupational exposure would be in the order of 2 years of exposure to the other components. Therefore, conservatively one can estimate about 2 year occupational exposure to be equivalent to a life time exposure to the other components and hence the last two components may be ignored. Consequently, if a population is chosen so that one or two dominant components of exposure to an agent can be identified and measured, an estimate of the dose to that may be considered considerably tractable. Unfortunately, for the converse case, i.e., if the dominance of a component of exposure to an agent cannot be identified, it is clear that relative consistency of the estimate can be determined only by the evaluation of all components of A and C, even if w_i and η_i can be assumed to be constants.

Conclusions and Implications

The theoretical development and the examples cited above, suggest that a relatively consistent estimation process for dose is possible, provided that the following criteria are met: (a) population at risk is selected such that the dominant components of concentration can be measured and translated to exposure; (b) for the population at risk selected, if there is no dominant component, then almost all components of concentration can be measured and translated to exposure. In general, the existence of dominant components suggests relatively "high" exposures, and, conversely, non-existence of dominant components suggests rela-

tively "low" exposures. Coupled with the analytical difficulties associated with the assessment of low concentrations, a dose estimation process for "low" exposures can not be readily assumed to be a simple and direct process. Therefore, even for a carefully selected population at risk (except for some unusually unique agents with unique responses) a study which is designed to determine dose-response relationships at low levels must include careful analysis of the components of the estimation process. If the measurements necessary for the estimation are impractical and a sound biological basis for extrapolation from populations exposed to "high" dose levels of that specific agent is not available, then the investigator is presented with a serious dilemma. Either the more relatively consistent estimate of "high" dose-response relationship is extrapolated to low doses without a sound basis, or the analysis of data is based on (on the dose estimation side) poor relative consistency where the level of response to an estimate of low dose cannot be readily justified.

The choice of basing an analysis on data with poor relative consistency, even though the data are at the levels where the measurement of the effect at those levels is the desired goal, presents a significant ambiguity and usually conclusions would be open to criticism. Conversely, the choice of extrapolation of results obtained at high dose levels to the desired level of dose without a sound biological basis may present the similar difficulties. Normally, the influence of the exposure magnitude on the route specific transport efficiency is not readily known and furthermore, the physiological basis for an extrapolation may not be clear. Under these circumstances, the extrapolation presents significant ambiguity and conclusions based on extrapolation would be open to criticism.

This dichotomy is presented graphically in Fig-

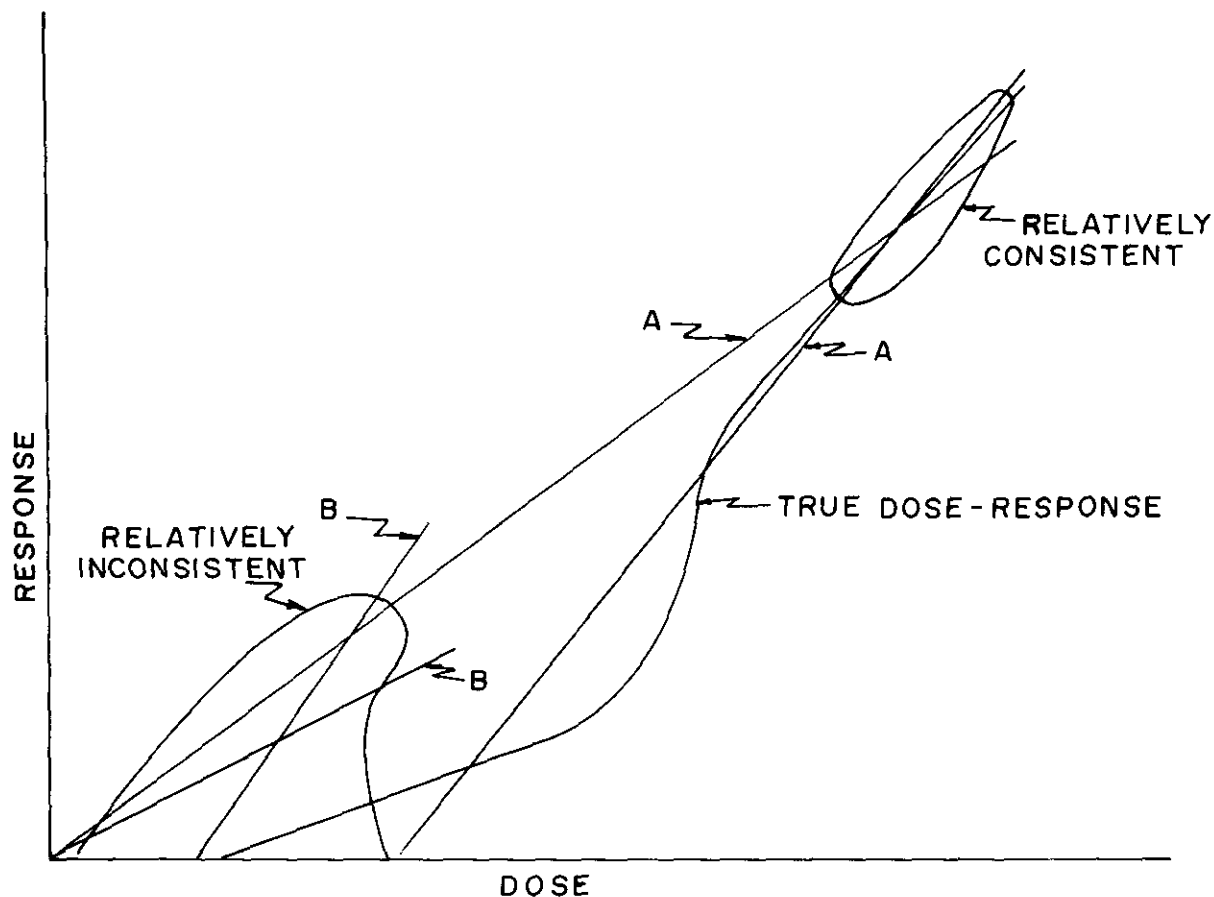


FIGURE 1. Graphical representation of the estimation/extrapolation dichotomy for a hypothetical dose-response relationship: (A) possible extrapolations; (B) possible regressions.

ure 1. Unfortunately, beyond glib clichés such as better experimental design, more fully characterized systems, this author is unable to present a resolution of this dichotomy. It is important to emphasize that there are many circumstances where, even at very low exposures, the relative consistency of the estimator is sufficiently good and that specific decisions on the dose-response relationship can be readily made. Therefore, the most important implication of the theoretical consideration reported here is that both the design and results of any study which aims to find a health effect or to construct a dose-response relationship must be fully scrutinized to see whether a

dose is tractable from the physico-chemical measurements made on the agent or extrapolation from a set of known (or observed) effects at high dose levels is feasible. If neither can be accomplished, to assign significance to the findings would be scientifically untenable.

REFERENCES

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